At-home STI specimen self-collection/ self-testing

At-home Specimen Self-Collection and Self-Testing for STI Screening Demand

Accelerated by the COVID-19 Pandemic - A Review of Laboratory Implementation Issues

Invited Mini-Review article for Journal of Clinical Microbiology

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The COVID-19 pandemic reduced STI testing volume due to social distancing and stay-at-home orders among other reasons. These events highlighted previously known benefits of at-home STI self-testing or specimen self-collection and accelerated testing demand via telemedicine. We review testing outside of traditional clinic settings. We focus on three curable bacterial STIs among the top 10 United States nationally notifiable conditions with screening recommendations: syphilis, gonorrhea (GC) and chlamydia (CT). At least 19 million GC/CT screening or diagnostic tests are performed annually, presenting a considerable challenge during the pandemic. Unlike for HIV, STI at-home tests are currently not commercially available. However, innovative telemedicine providers offer services where specimen self-collection kits are mailed to patients at home who then ship them to laboratories for processing. Laboratory-developed tests (LDTs) make this feasible, using FDA-cleared tests that have been modified and validated for self-collection outside the clinic setting. We discuss technical and regulatory aspects of necessary modifications for home-based specimen self-collection. The telemedicine provider typically manages and communicates results, provides linkage to care, and is responsible for billing and case reporting. We also describe rapid testing devices in development that may present an opportunity for future self-testing. In summary, COVID-19 has accelerated evaluation and development of STI self-tests and specimen self-collection. Remaining obstacles are high price, regulatory approval, support for laboratories offering the service and uncertainty whether target populations with greatest need are reached effectively. However, increased testing, convenience and privacy are potential benefits that may enhance uptake and outlast the pandemic.
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1. Introduction: The need is great

During the COVID-19 pandemic, many STI providers have become interested in telemedicine care models. They can reduce potential patient and staff exposure to SARS-CoV-2, while allowing provision of STI services. One obstacle is the need for laboratory testing and specimen collection. Before the pandemic, this typically necessitated a visit to a medical facility, even as fast and convenient STI care in express services (as described by the National Association of County & City Health Officials, [https://www.naccho.org/uploads/downloadable-resources/issue-brief_STI-Express-Services.pdf](https://www.naccho.org/uploads/downloadable-resources/issue-brief_STI-Express-Services.pdf)) or in pharmacies was already advancing. This mini-review provides a laboratory perspective and description of available technologies that could potentially be adapted into telemedicine models. Of note, the term “at-home” testing or collection has been perceived as excluding the homeless or incarcerated. In the context of laboratory diagnostic device terminology used by the FDA (Food and Drug Administration), it is meant to distinguish self-testing or self-collection under medical supervision from testing without such direct, in-person supervision. This is relevant as STI testing has advanced into non-traditional, often “non-clinical” settings like mobile vans, booths at health fairs or other communal sites. There, specimen self-collection can take place, but a medial professional is still present.

1a. STI testing before and during COVID-19

More than 2.4 million US cases of syphilis, gonorrhea, and chlamydia were reported to the Centers for Disease Control and Prevention (CDC) in 2018, according to CDC’s last available yearly surveillance report (1). The number included 1,758,668 cases of chlamydia (*Chlamydia trachomatis*, CT), 583,405 cases of gonorrhea (*Neisseria gonorrhoeae*, also known as the gonococcus, GC), and 115,045 cases of all stages of syphilis (causative agent, *Treponema pallidum*), including 35,063 cases of primary and secondary syphilis. Most alarmingly, congenital syphilis cases are rising and reached 1,306 cases in 2018. These statistics reflect not only diagnostic testing of symptomatic individuals, but also U.S. screening recommendations for these STIs which may often be
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present without symptoms. Asymptomatic screening reduces harmful sequelae such as adverse pregnancy outcomes, infertility, pelvic inflammatory disease (PID) and risk of HIV acquisition, among others. It is an integral component of HIV prevention. There are other viral, parasitic and bacterial STIs of concerning proportions and impact, e.g., HSV-1&2, Trichomonas vaginalis (TV), HPV, the emerging M. genitalium, and others. However, for bacterial STIs, CDC (2) and the US Preventive Services Task Force (USPSTF) (3) currently only recommend asymptomatic screening for chlamydia, gonorrhea and syphilis. Populations targeted for screening and screening frequency vary depending on risk. The screening recommendations cover, but are not limited to, sexually active young women under 25 years of age, pregnant women, men who have sex with men (MSM) and sexually active persons living with HIV (2). CDC recommends to screen for GC/CT by nucleic acid amplification testing (NAAT) using urine from men or vaginal swabs from women (4); additional screening at extragenital sites (throat and rectum) may be recommended depending on sexual history. Many commercial test products consist of dual GC/CT NAAT tests. Syphilis screening is recommended by serology, further discussed below (2). We here focus on screening for asymptomatic individuals; telemedicine management of symptomatic persons with suspected other STI is not within the scope of this review.

Data on actual annual tests performed are scarce. CDC only receives data on positive laboratory tests, not on negative tests. In 2016, Association of Public Health Laboratories (APHL) members responding to a survey reported performing 2,242,728 CT and 2,298,596 GC tests; this resulted in 12% and 16.8% of the nationally reported CT and GC cases that year, respectively (5). This would broadly suggest that on a national level with testing from other types of laboratories (commercial, academic, other public health or non-profit laboratories) between 14 – 19 million tests were performed for each disease in 2016. It is likely a substantial underestimation of current testing volume because test positivity may be considerably lower in commercial laboratories who often work with private providers rather than public STD clinics. Data on syphilis testing volume are even harder to estimate due to testing algorithms that require multiple sequential tests before a case report to CDC, and due to the use of different algorithms (see 4b. Considerations for modifications of syphilis testing with home self-collected blood).
1b. Evidence review for STI self-testing
The idea of specimen self-collection or self-STI testing is not new. In 2019, the World Health Organization (WHO) published the “WHO Consolidated Guideline on Self-Care Interventions for Health” as a first installment in a planned series for various diseases (8). The first document focused on “Sexual and Reproductive Health and Rights”. Self-care including self-testing has the readily apparent benefits of privacy, confidentiality, speed, convenience, and access if the price is affordable. It is “people-centered” (8) and enables active participation in one’s own health. It is also a health system approach as it can reduce burden on stretched systems with worldwide shortages in medical personnel or other barriers to health care access. Potential risks include: low specimen return rates, uncertain follow-up (linkage to care including treatment, repeat testing including test of cure, partner notification, counseling on risk reduction), unintended/unnecessary use (resulting in false positives with their own set of associated problems), incorrect use, lack of understanding of window periods (resulting in false negatives), lack of surveillance data generation, among other issues (8). The WHO systematically reviewed evidence for self-testing or specimen self-collection for GC, CT and syphilis, including US studies, and published a meta-analysis of available evidence (9). Programs offering self-collection of samples increased overall uptake of STI testing services (RR: 2.941, 95% CI 1.188 to 7.281) and case finding (RR: 2.166, 95% CI 1.043 to 4.498), prior to the pandemic (9). U. S. laboratory research on the equivalence and/or superiority of self-collected versus provider-collected specimens for test sensitivity was reported by Gaydos et al (summarized or referenced in (10)). Based on this evidence, WHO issued a new recommendation in 2019 “Self-
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collection of samples for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be made available as an additional approach to deliver STI testing services for individuals using STI testing services” (8). In addition, WHO issued a new and conditional recommendation: “Self-collection of samples for *Treponema pallidum* (syphilis) and *Trichomonas vaginalis* may be considered as an additional approach to deliver STI testing services for Individuals using STI testing services” (8). Thus, even before the COVID-19 pandemic, substantial expert agreement existed concerning benefits of this approach.

2. Overview of different telemedicine models during COVID-19

2a. Self-testing at home

Figure 1A schematically depicts two main STI self-care and testing models. In a self-testing model, the patient or consumer decides what test they want. They buy it commercially “over-the-counter” (OTC) or online without a prescription or medical provider order. They collect the specimen using instructions and materials packaged with the test. Next, they perform the actual test and read and interpret the result. Follow-up only happens if the patient decides to contact a clinic. This set-up is currently available for self-HIV test, but not for GC, CT, or syphilis testing as there are no such tests commercially available; current regulatory and technical hurdles are discussed below. This model may be best suited for diseases where individuals have definitive symptoms and can reasonably guess what test they may need. Numerous STIs cause overlapping symptoms such as itching, penile or vaginal discharge, anogenital ulcers or other symptoms that may prompt a desire for testing, as do exposure or risk behaviors. A consumer may order unnecessary tests at considerable cost (often >$100). A variation of this model are laboratories that operate independently, i.e., not in a telemedicine model. Rather, they accept self-collected specimens and testing requests directly from patients. A problem of such models is that some states have laws permitting only medical providers to order diagnostic STI tests and/or dispense laboratory results (11). There are also self-tests that require a prescription. Since none are available for STI, they are not further discussed here.
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2b. Specimen self-collection at home and submission to clinical laboratories after laboratory-developed test (LDT) validation

In a telemedicine model (Fig. 1B), a patient receives remote assessment and evaluation. The provider may use questionnaires or previously provided patient information to determine if the individual falls under a STI screening category before the visit. The facility then sends the patient an at-home specimen collection kit with instructions. The patient ships the specimen to a laboratory which offers a test accepting self-collected specimens (further described below). Results are reported back to the clinic or directly to the patient. When the patient subsequently interacts with the medical provider, laboratory results are typically already available, and he/she is already linked to care. Alternatively, testing can be ordered during the telemedicine visit as needed. Many versions of this set-up exist. For example, billing can be handled by the laboratory or clinic, collection kits could be sent by the clinic, laboratory or even a third-party commercial entity.


3a. Regulatory terms for clinical laboratory diagnostics

Brief definitions of relevant terms are also summarized in Table 1. Some confusion exists around the terms “self-testing” and “specimen self-collection”. In the U.S., the FDA regulates diagnostic testing and defines test labels. A “self-test” refers to a test that is FDA approved/cleared for patient performance in its entirety, meaning not just specimen collection and send-off to a laboratory, but also performing the actual test and reading the result. This would be clearly indicated as “intended use” in the product’s package insert. Reviewing the package insert and all other packaging inclusions such as specimen collection materials is an integral part of the FDA’s clearance process. A prescription may or may not be required to obtain the self-test. The provider can also send the test
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home to their client. The consumer then collects a specimen and conducts the test without direct medical supervision. The public is most familiar with home pregnancy self-tests, available in the US since the 1970s.

Furthermore, the distinction between “provider-instructed” and “at-home” self-collection is in part explained above. There are available STI tests where nuances are particularly relevant: Many available GC and CT NAAT are FDA cleared for specimen self-collection at a provider facility under medical supervision but not at home. This is stated in package inserts. During provider-instructed collection, the medical provider explains the process and potential risks in person, possibly with visual materials packaged with the kit, in accordance with the intended use of the kit. The patient then goes to a private clinic area to collect urine or a vaginal swab; other possible specialized swabs are rectal, throat and penile-urethral. Numerous studies have demonstrated that patient-collected samples have similar test performance to provider-collected samples (reviewed and summarized by Gaydos (10)). In the STI field, many GC/CT NAAT diagnostic devices include a provider-instructed specimen self-collection kit. Alternatively, the kit is available for purchase separately but clearly labeled for use with the diagnostic test. Typically, there is a collection instrument (e.g., a swab, a urine container), and a corresponding test tube with buffers/solutions that stabilize the collected material until testing. However, even such collection kits may not simply be used at home since this would be outside their intended use. If the materials were to be used at home, it would be necessary to conduct a “laboratory-developed test (LDT) validation” study as further detailed below.

The situation is slightly different for syphilis testing. Typical non-rapid laboratory-based serological syphilis tests accept blood, serum or plasma and do not typically contain specimen collection materials. They are designed for venipuncture by a medical professional. Universally available OTC blood self-collection kits, e.g. dried blood spots (DBS) and BD microtainers® (BD, New Jersey) can be purchased separately or provided by the LDT manufacturer and are discussed below.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) are regulations promulgated by the Centers for Medicare & Medicaid Services (CMS) (USCODE-2011-title42-chap6A-subchapII-partF-subpart2-
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207 sec263a.pdf (govinfo.gov). Their purpose is to establish quality standards for clinical laboratory testing to
208 ensure that patient test results are accurate and reliable. In the US, clinical laboratory testing is governed by
209 CLIA and requires activities such as documentation of staff training and proficiency, equipment calibration and
210 maintenance, and other quality measures. Laboratories are regularly inspected for their compliance with the
211 amendments and may only operate if they have a current CLIA certificate. CLIA federal regulations apply unless
212 the state has enacted laws relating to laboratory requirements that are equal to or more stringent than CLIA
213 requirements, e.g., Clinical Laboratory Evaluation Program in New York State. Compliance is achieved by
214 implementing all aspects of cleared tests as described in the package insert, and by verifying that the test
215 performs as expected in one’s local laboratory that is inspected by CMS and has a valid CLIA certificate. “CLIA
216 waivers” are discussed in the following paragraph. A “laboratory-developed test” (LDT) is a test that has not
217 gone through regular FDA review (exception: tests entitled for Emergency Use Authorization uses). CLIA permits
218 such tests if the local clinical laboratory director approves test performance data according to CLIA regulations.
219 Lab-developed tests can use FDA-cleared components, e.g., a cleared GC/CT NAAT diagnostic device, and modify
220 them, e.g., by accepting self-collected specimens. The process of lab-developed test validation for STIs in local
221 laboratories is described below.

222

3b. Terms for rapid tests, Point-of-Care Tests (POCTs), CLIA-waived tests

223 There are also “CLIA-waived tests”. They are simple to perform, carry a low risk of an erroneous result and
224 can sometimes be candidates for further development into self-tests. The CLIA-waiver designation is determined
225 by the FDA and is based on review of the manufacturer’s application and data submission. It indicates that the
226 test can be safely performed by non-laboratorians. Complexity of instrument operation and maintenance is
227 considered, among other factors. They are often rapid tests or “point-of-care” (POC) tests, or “single use
228 devices” (SUD), terms used interchangeably in this review and not further differentiated. However, not all rapid,
229 POC or SUD tests are CLIA-waived. And, CLIA-waived tests are not automatically approved for self-testing;
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generally additional trials and data submission are required for a test to be approved for self-testing. For example, the Syphilis Health Check (SHC) syphilis rapid test is CLIA-waived for testing using fingerstick whole blood specimens, while the Chembio DPP HIV-syphilis test is currently not CLIA waived as of manuscript submission. Furthermore, some CLIA-waived tests may not be suitable for self-testing. A typical reason is that it would not be feasible for an associated instrument to be used at home. It is also possible that the manufacturer has not collected and submitted data for FDA review to obtain this indication, among other reasons.

Fig. 1C shows a comparison of features often attributed to clinical laboratory tests, rapid and self-tests. Typically, clinical laboratory-based tests have features such as relatively long time to result, high instrument need, operator training need, quality control documentation need, high test performance metrics, high energy/internet usage, and great potential for electronic data export. Self-testing and even rapid tests may rank lower on these, but their price can be high, at least initially, reducing access (further discussed below in “6a. Lessons learned from at-home HIV self-testing”). The potential for linkage to care and for reaching people who may need testing is debatable and needs further evaluation. Since rapid tests are often designed as POC tests and have quick turnaround, their potential for linkage appears high. However, it is unclear how many people can get tested in a timely fashion, particularly if simple instruments run only one test at a time. The COVID-19 pandemic, or new express services, are expected to change how people access STI screening and testing.

4. Practical examples of STI laboratory services during the pandemic: How have some laboratories modified existing STI tests for acceptance of home-collected specimens?

When the COVID-19 pandemic unfolded, a few US laboratories were already able to accept at-home self-collected specimens. These were mainly commercial laboratories who had introduced the technology in prior years, as well as academic research centers. CDC and partners made lists of available laboratories for communications with HIV or STD service providers during the pandemic (https://www.cdc.gov/hiv/testing/self-testing.html; https://www.cdc.gov/std/prevention/disruptionGuidance.htm;
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https://www.ncsddc.org/resource/covid-command-center-for-std-programs/). The goal was to give rapid technical assistance to partners; it did not constitute endorsement, completeness, or quality assurance. How was it possible for the offerors to receive approval for such LDTs by the CLIA director? We will give examples how LDT validation can be done for GC/CT NAATs or syphilis tests. The APHL/CDC STD Steering Committee published a “General Checklist for Establishment of Performance Specifications for Tests Not FDA-Cleared or Approved” (https://www.aphl.org/programs/infectious_disease/std/Documents/ID_2009Oct15_Checklist-STD-Performance-Specs.pdf). This 2009 document contains practical advice from STI public health laboratory experts for STI test modifications.

4a. Considerations for modification of GC/CT NAAT for at-home specimen self-collection

Laboratory-based GC/CT NAAT testing is typically done with high-throughput, automated instruments (12). Laboratories are likely interested in keeping their established instrument. There are precedents of LDT modifications of these tests for extragenital specimen acceptance, as older generation tests were initially not cleared for their acceptance (13). The overall validation purpose is to ensure that test performance specifications are not substantially reduced by modification. For GC/CT home self-collection and submission to a laboratory, deviation from the approved package inserts exist in two main areas: a) lack of medical oversight during at-home specimen self-collection, and b) preservation of specimen integrity due to handling, temperature variation or delay in transit to a distant laboratory. A laboratory will need to show that test results are comparable in both clinic-based and home-based settings, among other local issues the CLIA laboratory director wishes to address.

For potential problems with obtaining the specimen at home, such as safety or incorrect specimen harvest, a remote provider can instruct a patient similarly over the phone or video-assisted secure technology as could be done in person at a medical facility. Some successful providers have made videos (e.g., Emory University Center for AIDS Research https://vimeo.com/138977095) or included visual materials in the mailed kit, or included materials that may make sample collection more convenient, such as foldable urine cups or
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cardboard tube stands. They can establish a contact mechanism, e.g., a phone number or hotline, should unforeseen problems arise. A test developer can also reference the substantial literature demonstrating successful self-collection (10).

The second validation goal is to document test accuracy when the patient performs initial specimen processing and initiates transport. The text below describes an example for urine collection for the Aptima Combo 2 test (https://www.hologic.com/sites/default/files/2019-12/502446-IFU-PI_009_01.pdf), the most often used NAAT in public health laboratories (12). The patient obtains first-catch urine using the provided cup. For initial sample stabilization, the patient would then follow the package insert instructions, i.e. “transfer 2 mL of urine into the urine specimen transport tube using the disposable pipette provided”, then “transport the processed urine specimens...at 2°C to 30°C and store at 2°C to 30°C until tested. Processed urine specimens should be assayed with the Aptima assay within 30 days of collection.” It is also possible to give the patient easier-to-read materials that still convey the procedure. The laboratory preparing the test validation plan and data could conduct a research study. However, enrolling human subjects in research studies to collect two specimens in parallel (one at home, one at a medical facility), obtaining their consent, and other study provisions may not be feasible for every laboratory, particularly during the pandemic. It is important to not over-interpret requirements for test validation, as suggested by the Association of Public Health Laboratories (APHL) who described examples of STI test validations (https://www.aphl.org/programs/infectious_disease/std/Documents/ID_2009Oct15_Checklist-STD-Performance-Specs.pdf). The document describes using spiked specimens may be used for the validation. Alternatively, left-over specimens from laboratories that have already obtained validation, or from commercial sources, can be used. When spiking specimens, “the matrices should be true specimens” (e.g., left-over urine or materials from swabs). Laboratories may over-estimate the number of specimens needed for a successful validation. The APHL document specifies “A minimum of 10 positive and 10 negative previously characterized specimens should be tested... Ideally, a total of 30 specimens should be tested....”. Therefore, a laboratory may expose 30 spiked specimens to local shipping conditions and compare their test results to a specimen aliquot.
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Without shipping. The laboratory may also ask non-laboratorians to perform initial sample processing steps using spiked specimens, for comparison to aliquots handled by laboratory professionals. Furthermore, the laboratory can develop specimen integrity acceptance criteria, e.g., they can stipulate kit return within 30 days or sooner. Some laboratories include a checklist for the patient to mark that they shipped the specimen under climate-controlled conditions rather than leaving it in their home mailbox exposed to weather. The greatest laboratory need is often for technical assistance with provision of left-over or spiked samples. Due to protections of human subjects in research studies, there is a requirement that personal identifiable information (PII) is removed from left-over specimens. This requires review, approval and documentation and may be beyond the capacity of some public health laboratories and associated infrastructure, particularly during the pandemic. The CDC STD Laboratory has been contacted repeatedly to provide left-over samples and is working with partners to develop a panel of suitable specimens to assist in future validation needs.

4b. Considerations for modifications of syphilis testing with home self-collected blood

Currently recommended syphilis diagnosis consists of clinical evaluation supported by laboratory testing for treponemal and non-treponemal antibody tests from whole blood, serum or plasma (2). The tests are done in sequence with the traditional algorithm (non-treponemal test first) or reverse algorithm (treponemal test first). Once a person has had syphilis, treponemal tests typically stay positive for life, even after treatment. In contrast, non-treponemal antibodies wane over time after treatment, often indicate current infection, and are used to follow treatment success. Treponemal tests in general have fewer technical challenges. They were the first to become widely available in automated format. On the other hand, non-treponemal tests are more technically challenging, in part due to lipid antigen – antibody recognition, the manual nature of the tests, subjectivity of result interpretation, and titer need for reactive specimens. Given the efficiency afforded with automation and high throughput, some laboratories prefer to perform treponemal tests first. This may be beneficial for settings conducting high-volume screening of populations at low risk for syphilis, e.g., prenatal screening. However, in high-seroprevalence populations of people with prior syphilis and high treponemal antibody positivity, e.g., men...
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who have sex with men who may require frequent screening, beginning with non-treponemal testing would be preferred. FDA-cleared automated nontreponemal tests have recently been introduced in the US and might help with expediting syphilis screening (14).

New technical issues are arising for self-collected specimens. DBS have been considered due to easy transportation and limited blood volume needed. The TPPA treponemal test performs well from DBS (15). Smit et al (16) demonstrated sensitivity and specificity of over 95% using TPPA-DBS when compared to TPPA-plasma specimens. There are commercial laboratories that offer complete DBS-treponemal test kits for at-home self-collection and shipping to a central laboratory. They include all needed supplies (blood collection card, collection and handling instructions, single-use lancets for finger pricking, alcohol pads, gauze pad, bandages, biohazard bags, supplier contact details). Unfortunately, however, DBS are not easily suitable for non-treponemal tests and might yield reduced sensitivity (unpublished data of the authors). To our knowledge, no U.S. laboratory has successfully validated such testing. Titers are required for all reactive non-treponemal tests to monitor infections. Quantitative testing is a challenge when antibodies are not sufficiently eluted from DBS. Some telemedicine providers have instead used blood finger-prick self-collection into OTC BD microtainers® (BD, New Jersey) to transport blood in liquid form before processing at a laboratory. However, a blood volume of 250-600 ul is needed. Self-collecting this high blood volume is a significant hurdle and may lead to lack of kit return.

As with all syphilis test validations, inclusion of specimens from all disease stages is a consideration when establishing performance characteristics to demonstrate equivalent results obtained using routine specimens. Validation studies exist for treponemal tests with paired testing of DBS and venous blood (15) and could be expanded with BD microtainers®, preferably from the same subjects. Forty to 100 or more samples have been considered for similar DBS comparison experiments (17). It is important to establish and validate the stability of self-collected specimen at storage temperature and time, humidity (applicable to DBS) and transport conditions (17). The CDC and APHL recently opened a characterized syphilis serum specimen bank (18). These
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available specimens can be mixed with freshly collected blood (nonreactive for syphilis), subjected to DBS or BD microtainer® handling and shipping conditions and be tested in conjunction with regularly processed specimens.

During the pandemic, a few solutions have emerged: To our knowledge, some laboratories offer treponemal testing from DBS, but not non-treponemal tests. If reactive, they call persons in or refer them for further blood collection and non-treponemal testing. This may work for test populations where syphilis rates are low. Some STD programs are currently only offering GC/CT testing remotely and if any syphilis test is indicated, the patient is asked to attend in person or is referred elsewhere.

5. A look ahead: Are new tests on the horizon that could be adapted for home use and what hurdles exist?

5a. Modification of existing laboratory-based tests

Could laboratory-based GC/CT NAATs be FDA-cleared to accept self-collected specimens permanently? This could be an attainable, near-term solution if a test developer takes the initiative to collect and submit data to the FDA and applies for clearance of at-home specimen self-collection as intended use of the test. The benefit would be to render it unnecessary that each laboratory conduct LDT validation experiments. It would widely allow the implementation that emerged as the most workable solution for GC/CT testing during the pandemic.

Laboratories without resources for LDT validations could then participate in telemedicine models and contribute to the nation’s testing needs in an era of persistently rising STI cases. After FDA clearance, each implementing laboratory would still conduct verification of test performance according to CLIA regulations, including documentation that a test ordering and result reporting process is in place. It is possible that data from laboratories with LDT and collected during the pandemic could serve as a portion of such an application for FDA review and additional data may be required. It is currently unclear whether additional performance quality controls would be needed when cleared lab-based or rapid tests are modified to accept such specimens, e.g., to mitigate the risk of false-negative tests. However, there is already evidence that self-collection of urine and
genital swabs are on par with physician collection for STI testing (10). Experiences during the pandemic may increase available evidence further.

5b. Modification of GC/CT rapid tests

Rapid and POC tests sometimes have potential for adaptation to self-testing. Table 2 provides a summary of the landscape of rapid STI test development for the US market, as it is known to the authors. We will discuss whether the tests are suitable for further development into self-tests. Several tests are in development and nearing market for settings like express clinics including pharmacies or outreach settings.

The Cepheid GC/CT GeneXpert test (Cepheid, Sunnyvale, CA) was the first rapid NAAT to receive US clearance in 2012. Since 2019, its intended use is also cleared for extragenital specimens (13). US “express clinic” models (https://www.naccho.org/uploads/downloadable-resources/issue-brief_STI-Express-Services.pdf) have almost exclusively used this test, as it was the only same-day testing system available for many years. The test is typically performed on site, e.g., at an STD clinic, with a 90-minute turnaround time. The FDA cleared it as “moderately complex”, meaning it requires trained staff and generally some laboratory equipment such as precision measuring devices (pipets). It is currently not available as CLIA-waived test. For other disease diagnostics, however, Cepheid has adopted their technology to “GeneXpert Xpress” status as CLIA-waived tests, i.e., for Influenza, RSV, Strep A. It may become available for STIs in the future. Its adaptation to home usage is unlikely in its current formats since the instrument cannot easily be sent home.

The Binx io (Binxhealth, Cambridge, MA) molecular rapid point-of-care test was FDA-cleared in 2019, and takes only 30 min (https://mybinxhealth.com/news/binx-health-receives-fda-510k-clearance-for-rapid-point-of-care-platform-for-womens-health). It requires a small, movable, desktop instrument which was initially not yet readily available for sale. The test needs single-use GC/CT cartridges that contain all reagents. It accepts male and female urine and vaginal swabs, and no pre-processing is needed. The test is currently not cleared for extragenital specimens unless an additional lab-developed test modification is done. On March 30, 2021, the FDA allowed the use of the test under a CLIA Certificate of Waiver, allowing use in near-patient point-of-care
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Adaptability to self-testing at home faces the challenge that the instrument is not suitable to be sent home. Of note, an additional rapid GC/CT NAAT by Visby Medical is in late stage development (19). It consists of a hand-held, disposable, low-cost device and may thus be suitable for home use or non-clinical setting if it becomes available. Other devices may also be nearing the market; of note, data submission to FDA for clearance review is not public information.

Sc. Modification of Rapid Syphilis Testing

The Syphilis Health Check (SHC) test is a rapid test cleared for use in the US. It detects treponemal antibodies and can be performed on whole blood as well as plasma or serum. It is CLIA-waived for fingerstick whole blood specimens and can thus be used in outreach settings. It is not currently approved for self-testing. Test kits do not include blood collection or fingerstick materials like a lancet. There are currently no published studies evaluating self-usage to our knowledge. The test requires three drops of blood; the first is contaminated with alcohol and is discarded, and the next drops are collected in a pipette and applied to the device. Reading the test result precisely at the prescribed time, i.e., 10 not exceeding 15 minutes is critical for accuracy of results and has caused false positive results even when performed by trained laboratorians (20). Chembio’s DPP HIV-syphilis (treponemal) test has recently received FDA-clearance (https://www.fda.gov/media/142615/download). This rapid test detects antibodies to HIV (type-1 and 2) and T.pallidum bacteria in fingerstick whole blood, venous whole blood (potassium EDTA), or plasma specimens (potassium EDTA). It requires a small, hand-held optical reader and is currently not CLIA waived or approved for self-testing.

Internationally, several other rapid antibody tests are in use, as recently reviewed by Toskin (21). They may potentially be purchased and validated as LDT. Some syphilis tests include both a treponemal and non-treponemal component, other popular tests are HIV-syphilis dual tests. The latter tests most commonly are
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implemented internationally for ante-natal testing for prevention of mother-to-child transmission of both infections, where long wait periods and potential loss-to-follow-up would be disastrous to the infant.

6. Discussion and areas of greatest need for additional knowledge

6a. Lessons learned from at-home HIV self-testing

HIV self-testing uptake increased in the pandemic according to some reports (22), due to the one available HIV self-test, i.e., the OraQuick™ from OraSure Technologies. The long road to test uptake, reviewed by Stevens et al (23), might offer insights for STI self-test development and marketing. A precursor test was first introduced in 1996 as OTC home self-blood collection kit followed by submission to a laboratory. It was modified to fingerstick blood rapid test, but only gained acceptability when oral fluids were shown to be an acceptable sample type in 2004. Finally, in 2012, the OraQuick test was approved for in-home use as a self-test but had slow uptake. Thus, the development timeline spanned decades. This suggests that interim solutions are necessary for STI testing. It also provides examples how to prevent a similarly long timeline for STI testing. Issues around pricing and reimbursement are important, numerous and can only be addressed superficially in this laboratory review. Suffice it to say that the current OTC price (~$40) is a major hurdle to the use of the OraQuick test. One conclusion is that avoiding direct cost to patients is an important consideration, perhaps by requiring a prescription or by sending the test home. A discussion of insurance coverage and reimbursement by insurance companies was beyond the scope of this article but is nonetheless essential.

Blood self-collection is another considerable hurdle. Therefore, developing an oral or urine syphilis test would be ideal. Molecular methods can be used to detect Treponema pallidum ssp pallidum in the mouth (24) and protein antigens are detectable in urine (25) albeit more technical development is required.

6b. Areas of greatest need for additional knowledge on STI testing
For STI screening, telemedicine models emerged as a workable model. In addition to already discussed benefits, cost to patients and proper test selection are mitigated when the providers select testing as indicated and bill patients’ insurance plans, reducing potential out-of-pocket cost. Lastly, syphilis, gonorrhea, and chlamydia are nationally notifiable diseases; diagnosing them at home would likely result in non-reporting. Telemedicine providers on the other hand, have developed procedures for mandated public health reporting. The pandemic caused a STI test kit and reagent shortage (CDC, https://www.cdc.gov/std/general/DCL-
Diagnostic-Test-Shortage.pdf) in the 3rd and 4th quarter of 2020 and stretched the limits of the public health and other laboratory workforce. It affected STI testing volume and limited test format choices in all settings. The shortage was not further discussed in this article. It is acknowledged that it may have caused STI testing after home specimen collection through online offerors out of necessity, e.g., laboratories typically associated with STD clinics were overburdened with COVID-19 testing.

Many other aspects of STI telemedicine and testing need further evaluation; some policy areas are out of the scope of this review. For example, studies on access in rural areas are needed. Low kit return rates may be an issue, however it is currently unclear if blood self-collection is the main cause. Previous studies of kit return rates and associated factors may inform improvements (26). Even so, unreturned devices are inexpensive and lab services are not actually billed if no specimen is shipped. Staffing of shipping, phone or other hotlines for people using at-home collection kits, and other patient services can be an issue, particularly during the pandemic when health provider systems are stretched. Shipping delays occurred during the height of the pandemic and during Holidays. Another concern is that at-home receipt of materials suggesting STI infection may not work for people with need for privacy from their family or co-habitants, possibly due to partner violence and fear of family members unaware of sexual activities or preferences. Workarounds like pick-up locations are possible. The pandemic has also reignited conversations about the digital divide in this country – some populations may not have access to technologies that enable telemedicine, i.e., computers, internet and cell phones. Therefore, a remaining question is whether people in greatest need of testing are reached with
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Telemedicine provision of services? Other open questions remain around need for confirmatory testing, timely care, and impact on rescreening rates.

7. Summary

Even before the COVID-19 pandemic, there was a growing movement in the STI field to work towards specimen self-collection at a minimum, and ideally also towards complete self-testing. Perhaps the greatest benefit is that it allows convenience, privacy and gives the patient an opportunity to avoid embarrassment while still accessing STI care. Increasing access to STI testing is a key strategy to mitigate continuously rising STI rates, particularly congenital syphilis rates. The pandemic and need for social distancing have accelerated and increased the urgency of this need. While workable laboratory solutions are emerging for GC/CT testing, syphilis testing remains challenging, and will require additional research and evaluation effort by laboratories to optimize self-collected testing for this disease.

Figure 1 Legend

A. A self-testing set-up. There are currently no “over-the-counter” syphilis, gonorrhea or chlamydia tests available but one exists for HIV testing.

B. A telemedicine model for STI testing as commonly developed during the COVID pandemic. In this model, the patient typically does not pay out of pocket for laboratory testing. The laboratory accepts home self-collected specimens because it has conducted a lab-developed test (LDT) modification, i.e., test validation under supervision of its clinical laboratory director.

C. Continuum of test features of laboratory-based, rapid POC, or self-tests. POC = point-of-care.
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We thank members of the COVID-19 NCHHSTP HIV, STI, Hepatitis self-testing TIGER team for insightful discussions. We thank members of the HHS COVID response Joint Commissioned Cell Testing and Diagnostic Work Group for sharing their knowledge of CLIA waivers. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

No conflicts of interest. Funded by CDC.
Table 1: A glossary of test descriptions with relevance for STI at-home testing or specimen collection

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA cleared test</td>
<td>A testing device that has been cleared by the FDA for use in the US. All FDA cleared tests are manufactured with a package insert that specifies their use including acceptable specimens and their collection method.</td>
</tr>
<tr>
<td>Self-test</td>
<td>A device that an individual can obtain with prescription or over-the-counter, possibly by mail. The package insert indicates self-testing as intended use. The individual then conducts specimen collection and the test on their own using instructions from the insert and gets results without shipping anything to a laboratory or waiting for results.</td>
</tr>
<tr>
<td>Provider-instructed specimen self-collection kit</td>
<td>A collection kit/device sold with a package insert that specifies that a medical provider will instruct an individual how to use the kit at a medical facility. Many GC/CT NAATs are FDA cleared for this type of specimen self-collection, e.g., for urine and vaginal/rectal/oral swab self-collection. The facility’s staff then typically submits the specimen to an associated laboratory or performs a test.</td>
</tr>
<tr>
<td>At-home specimen self-collection kit</td>
<td>A collection device that is meant for use at home or away from a medical provider facility without in-person instruction by a medical provider. The self-collected specimen is then shipped to a laboratory and results are communicated at a later time. There are currently no FDA-cleared GC/CT or syphilis tests that include such a component. LDTs with at-home specimen collection devices are increasingly offered.</td>
</tr>
<tr>
<td>CLIA regulated test</td>
<td>The Clinical Laboratory Improvement Amendments of 1988 (CLIA) are regulations governed by the Centers for Medicare &amp; Medicaid Services (CMS). Their purpose is to establish quality standards for clinical laboratory testing to ensure that patient test results are accurate and reliable. Clinical laboratory testing is governed by CLIA and involves activities such as documentation of staff training and proficiency.</td>
</tr>
<tr>
<td>At-home STI specimen self-collection/ self-testing</td>
<td></td>
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<td>--------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Lab-developed test (LDT)</strong></td>
<td>A test that has not gone through regular FDA clearance (exception: Emergency uses) but can nevertheless be performed at local laboratories. CLIA permits this if the local clinical laboratory director reviews and approves test performance data according to CLIA regulations. LDTs can use FDA-cleared components (e.g., a GC/CT NAAT) modified to accept self-collected specimens. Validation data are necessary showing that collection and shipping methods result in acceptable test performance.</td>
</tr>
<tr>
<td><strong>POC and/ or rapid test</strong></td>
<td>Point-of-care test. A test that is designed to be performed rapidly at a medical provider facility while the patient waits. The term implies that results are available for treatment decisions. This is as opposed to a test performed after specimen submission to a laboratory. Some rapid tests can be performed at POC but also outside of medical provider facilities.</td>
</tr>
<tr>
<td><strong>CLIA waived test</strong></td>
<td>A test device maker can apply for the label “CLIA waived” during FDA clearance review. It indicates that the test can be safely performed by non-laboratorians, typically due to its simplicity. CLIA-waived tests can be good candidates for self-testing but are not automatically approved for self-testing. Some CLIA-waived tests still require equipment that cannot be transported to a home and thus cannot be adapted for home self-testing.</td>
</tr>
</tbody>
</table>
### Table 2: Landscape of STI tests with relevance for future home testing or self-collection pending further development

<table>
<thead>
<tr>
<th></th>
<th>Gonorrhea (GC)/ Chlamydia (CT)</th>
<th>Syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC recommended main diagnostic or screening test</td>
<td>GC/CT NAAT from urine (men) and vaginal swab (women).</td>
<td>Sequential treponemal or non-treponemal antibody detection in blood</td>
</tr>
<tr>
<td>Is a self-test* currently available in the US?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Is a specimen collection kit/device** available that can be shipped to a home or dropped off at central site?</td>
<td>Yes, but subsequent testing needs lab-developed test validation.</td>
<td>Yes, but subsequent testing needs lab-developed test modification.</td>
</tr>
<tr>
<td></td>
<td>Many commonly used NAAT tests are FDA cleared for clinician-instructed, self-collected specimens (urine, vaginal/rectal/pharyngeal swabs). The tests have corresponding easy-to-use collection kits that can be mailed to homes.</td>
<td>Available methods:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) Universally available blood self-collection devices such as BD Microtainers®.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Dried Blood Spots (DBS) can work for treponemal antibody detection but are problematic for non-treponemal tests (e.g., RPR)</td>
</tr>
<tr>
<td>Existing CLIA waived tests</td>
<td>Binx io NAAT; 30 min (as of March 2021)</td>
<td>Syphilis Health Check™, a rapid qualitative test for the detection of antibodies to <em>T. pallidum</em>; 10-15 mins; visual reading of results</td>
</tr>
<tr>
<td>Existing POC or rapid tests w/o CLIA waiver***</td>
<td>Cepheid GeneXpert NAAT; 90 min</td>
<td>Chembio HIV/Syphilis (treponemal antibody); a rapid qualitative multiplex test for the detection of antibodies to HIV/<em>T. pallidum</em>; 15-25 mins;</td>
</tr>
</tbody>
</table>
At-home STI specimen self-collection/self-testing

Legend:

**Self-test** refers to a test an individual can obtain, perform, and get the results back without shipping a specimen back to the laboratory and waiting for results.

**Specimen collection kit/device** refers to a test an individual can obtain. The person can perform urine, blood spot, or other specimen collection, ship the specimen to a laboratory and receive results over the phone/internet.

*** The GeneXpert technology has been adapted to a CLIA-waived “Xpress” instrument, however, to our knowledge, this is currently not available for GC/CT testing. Criteria used here: 90 minutes or less and up to moderate complexity.
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References

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At-home STI specimen self-collection/ self-testing


A. Self-testing model

Home test kit "Store"

B. Telemedicine model

RX "Clinic"

Home sample collection "Laboratory"

C. Continuum of test features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Lab-based test</th>
<th>Rapid test</th>
<th>Self-test</th>
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</thead>
<tbody>
<tr>
<td>Time to result</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Instrument need</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Operator training</td>
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<td></td>
<td></td>
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<tr>
<td>Quality control documentation</td>
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<td></td>
<td></td>
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<tr>
<td>Sensitivity and specificity</td>
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<td></td>
<td></td>
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<tr>
<td>Price</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Energy source or connectivity needed</td>
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<td></td>
<td></td>
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<tr>
<td>Data export</td>
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<td></td>
<td></td>
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<tr>
<td>Potential for linkage to care</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Potential for reaching people who need testing</td>
<td>?</td>
<td>?</td>
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